REMARKS

In response to the final rejection of May 2, 2007, Applicants submit herein an amendment and a Request for Continued Examination (RCE). By virtue of the filing of a RCE, the amendment is entered into the application. Favorable reconsideration of the application is respectfully requested in view of the above amendment and following remarks.

Claims 1, 7-8 and 13 are pending in the application. Claims 1, 7-8 and 13 have been rejected. Claims 1 and 13 have been amended. No new matter has been added.

Claims 1, 7-8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lobaccaro et al., J. Med. Chem, Vol 40, pp. 2217-2227, 1997 (Lobaccaro et al.).

Applicants traverse the rejection and respectfully submit that Lobaccaro et al. do not make obvious amended independent claims 1, 8 and 13. Arguments previously made in the response dated February 20, 2007 are herein incorporated by reference. In particular, Applicants below address specific statements the Examiner made in the outstanding Action with respect to Lobaccaro et al.

The Examiner states that

> Applicants further argue that the claimed compounds are not obvious over the teaching of Lobaccaro et al., because the claimed compounds "do not possess similar properties to the compound taught by Lobaccaro et al" (see page 8 of Remarks submitted February 20, 2007). In particular, Applicants point to Table B of their specification which they assert shows ERα/ERβ agonist activity for compound 2, which they assert is compound 5b of Lobaccaro et al, and which is in contrast to compound 3, (Included in the compounds recited in claim 1), having ERα agonist/ERβ antagonist activity. The Examiner notes that the motivation for providing the C5 homolog in place of the 5b compound of Lobacarro et al. rests on an expectation of similar ER agonist activity (Lobaccaro et al. does not specifiy whether the estrogen receptor is ERα or ERβ). The results shown by Applicants in

> Table B of their specification actually confirm this assumption, as both the compound 5b and the C5 homolog exhibit ERα agonist activity. Accordingly, it is considered that one of ordinary skill in the art at the time of the invention would have found it obvious to provide the homolog with the expectation of achieving an "estrogenic" compound.[see outstanding Action, paragraph bridging pages 10-11.]

In response, it is noted that both compound 2 and compound 5b in Lobacarro et al. both possess a 4C R group(R=butene). The Examiner appears to be uncertain that compounds 2 and compound 5b are the same. To this end the Examiner is requested to specifically point out how compounds 2 and 5b are structurally dissimilar. Further, while the C4 compound 2 and the C5 homolog, compound 3, possess a similar property, ERα agonist activity, one skilled in the art would not have reasonably expected that compound 2 and compound 3, would also possess a dissimilar property (compound 2, ERβ agonist activity versus compound 3, ERβ antagonist activity). Accordingly, one skilled in the art would have expected, i.e., predicted, compounds 2 and 3 to both possess ERα agonist/ERβ agonist activity, which is not the case.

In *KSR International Co. V Teleflex Inc*, 82 USPQ2d 1385 (2007), the Supreme Court pointed out that predictability is an important feature in an obviousness determination. As discussed above, one skilled in the art would not have predicted that the C5 homolog, compound 3, would possess ERβ antagonist activity instead of the ERβ agonist activity possessed by the C4 compound, compound 2.

The Examiner also states

> However, as the compound 5b of Lobaccaro et al. differs from the instantly recited compound by only a methylene or ethylene group, that is, Lobaccaro teaches a C4 chain wherein the instant compound include C5 chains, it is considered that the instantly claimed compound are homologous to the compound of Lobaccaro et al., and thus are expected to have similar properties to the compound as taught by Lobaccaro et al, such as estrogenic activity. Thus, it is considered that one of ordinary skill in the art would have found it obvious to provide the C5 homologs of the Lobaccaro et al. C4 compound with

> the expectation of providing a compound with similar properties.[see outstanding Action, page 4, second full paragraph.]

In response, as stated above, while one skilled in the art may have found it obvious to provide a C5 chain in view of Lobacarro teaching that the C4 chain compound has "estrogenic activity", one skilled in the art would not reasonably expect that the C5 chain compound would possess a different property from the C4 chain compound (compound 2, ERβ agonist activity versus compound 3, ERβ antagonist activity).

The Examiner also states:

> Regarding the recitation the compound has "ERα agonist activity and ERβ antagonist activity' as recited in claims 1 and 13, it is respectfully pointed out that the recitations have not been given patentable weight because the recitation occurs in the preamble.

In response, claims 1 and 13 have been amended to add the limitation "ERα agonist activity and ERβ antagonist activity" to distinguish these compounds over the Lobaccaro compounds, in that the presently claimed compounds possesses a property not possessed by the Lobacarro compound. With respect to functional limitations in composition claims, it is noted that in *In re Sullivan* (decided August 29, 2007), the Federal Circuit, with respect to the claimed antivenom pharmaceutical composition as set forth below:

> An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifcailly to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the Crotalus genus [emphasis added with underline],

considered the functional limitation "wherein said antivenom pharmaceutical composition neutralize the lethality of the venom of a snake of the Crotalus genus" when assessing patentability of this claim.

It is respectfully submitted that in presently amended claims 1 and 13, the functional limitation, "ERα agonist activity and ERβ antagonist activity" imparts patentability to amended claims 1 and 14 over the prior art as such a property would not have been predicted by a person of ordinary skill in the art when reading Lobaccaro. Indeed, since Lobaccaro et al. is completely silent about distinguishing between the ERα and the ERβ receptor, and as the Examiner states "Lobaccaro et al. nonetheless teaches that the compound 5b, which is alkyl substituted (butene group) without an electrophilic group, is "estrogenic,", i.e., an estrogen agonist...", it is difficult to discern how the specific properties possessed by compound 3, ERα agonist activity and ERβ antagonist activity, can be obvious in view of the scant disclosure of Lobaccaro et al.

The Examiner also states:

> It is furthermore noted that the agonist and/or antagonist activity of a compound is a property thereof, and a product and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Accordingly, the composition and method rendered obvious by the references would, absent evidence to the contrary, meet the limitations pertaining to the ERα and ERβ agonist or antagonist activity used therein. [see outstanding Action, page 6, first paragraph].

In response, while a product and its properties are inseparable, evidence has been provided in Table A of the present specification, which clearly indicates that the properties possessed by the C5 compound (compound 3), ERα agonist activity and ERβ antagonist activity, are different from the properties possessed by the C4 Lobaccaro compound (compound 2), ERα agonist activity and ERβ agonist activity.

Accordingly, in view of the above arguments and previous arguments made in the response of February 20, 2007, it is believed that Lobacarro et al. does not make obvious claims 1, 8 and 13.

In view of the above, withdrawal of the rejection of claims 1, 7, 8, and 13 under 35 U.S.C. §103(a), is respectfully requested.

Claims 1, 2, 4, 7, 8, 13, 14 and 16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Napolitano et al., J. Med. Chem, Vol. 38, pp. 2774-2779, 1995 (Napolitano et al.).

Applicants traverse the rejection and respectfully submit that Napolitano et al. do not make obvious amended independent claims 1, 8 and 13. Arguments previously made in the response dated February 20, 2007 are herein incorporated by reference. In particular, Applicants below address specific statements made by the Examiner in the outstanding Action with respect to Napolitano et al.

With respect to Napolitano et al, the Examiner states

> Napolitano et al. teaches 11β-substituted derivatives of estradiol including ethynyl and propynl derivatives…Napolitano teaches that the compounds have high affinity for the estrogen receptor, and provides the affinities for compounds 2a (entry 3) having a propynyl group and entry 11 having an ethane group…Napolitano et al. teaches that the compounds can be used as tumor-imaging radiopharmaceutical...[see outstanding Action, paragraph bridging pages 6-7.]

In response, it is asserted that Napolitano is merely concerned with designing high-affinity probes for the estrogen receptor for imaging and is not at all concerned with assessing the specific type of estrogenic activity, i.e., ERα agonist or ERβ antagonist, possessed by the described

derivatives. It is further asserted that such an imaging agent is used as a diagnostic tool and is typically not used as a pharmaceutical for treating estrogen deficiency disorders as is presently claimed. While the Napolitano et al. compounds arguably are "radio-pharmaceuticals", use of the Napolitano et al. compounds as imaging agents (for binding to receptor) does not require that such diagnostic pharmaceuticals when bound to the receptor elicit a specific biological activity to treat a particular disorder. Indeed, Napolitano et al. is devoid of any teaching or specific suggestion that 11β-estradiol derivatives having the specific R11 groups (having a total number of 5-6 carbon atoms) as recited in amended independent claims 1, 8 and 13 would possess both ERα-agonist activity and ERβ-antagonist activity.

The Examiner also states:

> Furthermore, as Napolitano et al. teaches that the length of the 11β alkynyl side chain can effect the estrogen receptor binding affinity it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of length of the 11β alkynyl side chain of the compound, according to the guidance provided by Napolitano et al., to provide a composition having desired properties, such as desired estrogen receptor binding affinities. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." [see outstanding Action, page 8, first full paragraph.]

In response, it is noted that Napolitano et al. is directed to optimizing the binding affinity of estradiol derivatives as candidate receptor-based imaging agents (see whole article and page 2776, second column, conclusions, first paragraph). With respect to the length of the 11β alkynyl side chain, Napolitano et al. further conclude that an 11 β-ethynyl group (i.e., compound 3a/entry 5 in Table 1) has a higher binding affinity to the estrogen receptor than an 11 β 1-propynyl group (i.e., compound 2a/entry 3). Indeed, Napolitano et al. indicate on page 2776, second column, conclusions, first paragraph, that

> The effect of a 1-alkynyl group at the 11β position on binding depends on the length of the chain; with the ethynyl group, the binding increases, whereas with the higher homolog 1-propynyl group, it undergoes **a marked drop** [emphasis added in bold]....The possibility for markedly improving the binding affinity of moderately sized estradiol derivatives by placing a substitutent at the 11β-position has definite constraints, since the enhancement of binding appears limited to nonpolar groups whose volume is comparable to or lower than that of an ethyl group. **Therefore, as far as the binding affinity is concerned, in designing a receptor-based imaging agent, it will probably not be a useful strategy to use an 11β-group to improve binding and to provide a site for the incorporation of the label, if this will make the 11β-group too polar or too large**.

In view of the afore-mentioned Napolitano et al. disclosure, one skilled in the art would not be motivated to increase the chain length longer than C2 (ethyl), let alone up to C5 (as in the present invention) to optimize binding as asserted by the Examiner because Napolitano et al. teaches that the binding decreases upon increasing the chain length which would defeat the intended purpose in Napolitano et al. of developing an affinity label with improved binding. Indeed, it may be considered that Napolitano et al. teach away from the presently claimed compounds having the specified R11 carbon length.

In this regard, it is well settled that a determination of obviousness not only requires that the claimed invention be read as a whole, but also that the prior art reference be read as a whole and that:

> "consideration must be given where the references diverge and teach away from the claimed invention."
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> *Akzo N.V. v. United States Intl Trade Commission*, 808 F.2d 1471, 1481, 1 U.S.P.Q. 2d, 1241, 1246 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987).

The Federal Court has instructed that a prior art reference "teaches away" when one of ordinary skill, upon reading the reference, would be discouraged from following the path set out in

the prior art reference, or alternatively, would be led in a direction divergent from the path that was taken by the applicant. *In re Gurley*, 31 U.S.P.Q. 2d 1131 (Fed. Cir.1994).

In view of the above instruction, it may fairly be said that Napolitano et al., in teaching that the binding affinity markedly drops when increasing the chain length above C2 (ethynyl) specifically teach away from the presently claimed compound which requires a carbon length at R11 of 5 carbons. Accordingly, one skilled in the art armed with the teaching of Napolitano et al. would be led in a direction divergent from the path that was taken by the Applicants, that is, one skilled in the art would not have chosen to optimize the binding by increasing the chain length beyond 2C (ethynyl).

In view of the above arguments and previous arguments made in the response of February 20, 2007, it is believed that Napolitano et al. does not make obvious claims 1, 8 and 11.

In view of the above, withdrawal of the rejection of claims 1, 7, 8, and 13 under 35 U.S.C. §103(a), is respectfully requested.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, she is requested to call the undersigned at the number listed below.

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Respectfully submitted,

By 

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